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Informing Decisions About New Health Technologies

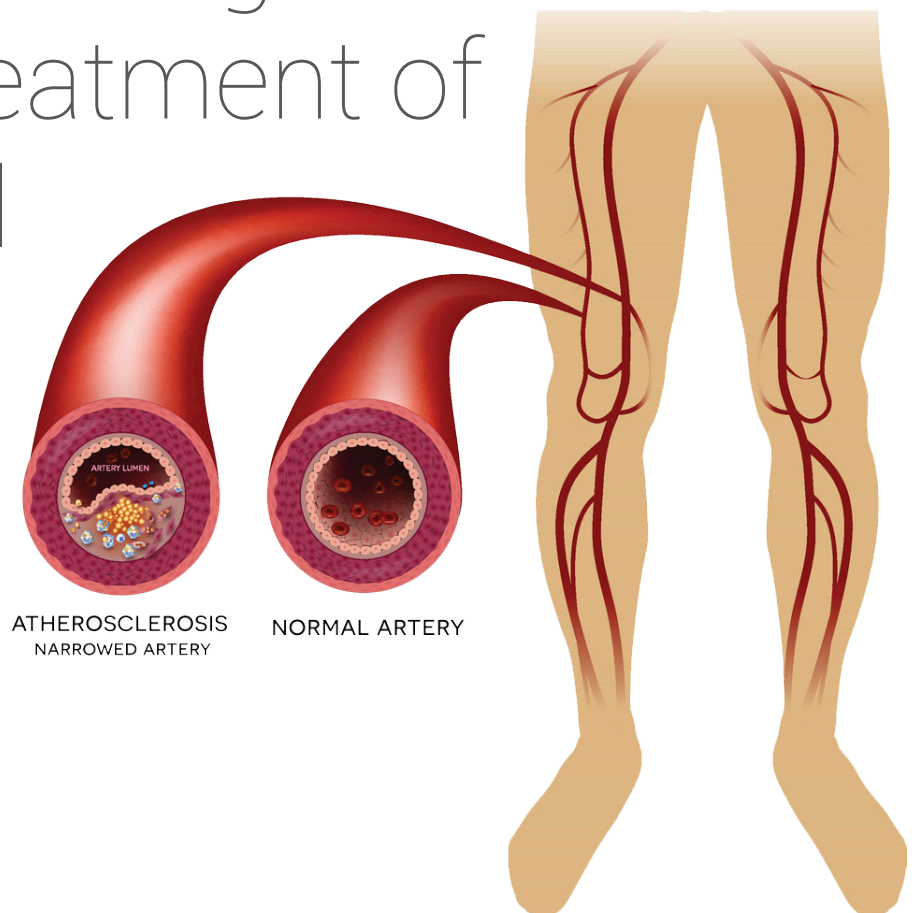
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New Technologies for the Treatment of Peripheral Artery Disease



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Summary

- Peripheral artery disease (PAD) is primarily caused by plaque in the arteries that supply blood to the body. It generally indicates systemic atherosclerosis and an increased risk for cardiovascular events.
- People with diabetes, those who smoke, the elderly, and those with cardiovascular disease are particularly at risk for PAD.
- This bulletin highlights some of the issues concerning PAD diagnosis and treatment in Canada, and summarizes the available information on two of the many new endovascular devices used to treat PAD in the legs:
 - **Shockwave Lithoplasty System** (Shockwave Medical): balloon angioplasty with lithotripsy (sound waves) to disrupt calcified plaque
 - **Pantheris Lumivascular Atherectomy System** (Avinger, Inc.): directional atherectomy guided by optical coherence tomography.
- Currently there is a lack of good quality, comparative evidence to guide clinical practice on many of the new endovascular technologies used to treat PAD.

Background

Peripheral artery disease is caused by atherosclerosis, or the build-up of plaque (fatty deposits) and calcification in the walls of the arteries. Most commonly, PAD affects the arteries that supply blood to the legs and feet.¹⁻³

As well as narrowing and blocking the arteries, the artery walls stiffen, preventing them from dilating to increase blood flow. Insufficient blood flow can result in cramping, leg pain, and muscle fatigue, that makes walking difficult and affects quality of life.^{4,5}

Individuals with symptoms of PAD may have either:

- **Intermittent claudication:** Claudication is leg pain, usually in the calf but sometimes the hip, buttock muscles or lower back, that occurs while walking or exercising and can cause limping.⁶ The pain is relieved at rest.^{7,8}
- **Critical limb ischemia:** Ischemia is inadequate blood flow causing insufficient oxygen supply. It is caused by severe PAD and is manifested by leg pain (even at rest), numbness, coldness or pain in the feet and legs, and non-healing leg or foot ulcers.⁷ Critical limb ischemia is a major cause of limb amputation.⁹⁻¹¹

About half of people who have PAD are asymptomatic, but whether or not it causes symptoms, PAD can indicate systemic atherosclerosis and an increased risk for heart disease and stroke.^{1,8,9,12,13}

Many new devices, and new generations of older devices, are now available for less invasive, endovascular treatment of PAD.^{14,15} This bulletin focuses on two of these new technologies, one an atherectomy device with enhanced imaging guidance and the other a type of balloon angioplasty combined with lithotripsy that may improve treatment of calcified lesions.

The Technology

Minimally invasive endovascular treatments to expand the opening of the artery, such as angioplasty or atherectomy, are now used more often than bypass surgery as the initial treatment approach for PAD.¹⁶ The two main types of endovascular treatments for PAD are:

1. **Balloon Angioplasty With Stenting:** Sometimes called percutaneous transluminal angioplasty, this procedure uses a balloon tipped catheter, advanced over a thin guide wire, and filled with contrast fluid to push the plaque against the wall of the artery, widening the opening to increase blood flow. Some of the newer angioplasty technologies also use a drug-coated balloon to reduce post-treatment cell proliferation or restenosis (when narrowing of the diameter of the artery recurs after treatment). A bare metal

or drug-eluting stent may also be inserted to try to prevent restenosis, but stents cannot always be used.¹⁷

Balloon angioplasty is performed using angiography (X-ray imaging with contrast media to show blood flow). Increasingly, balloon angioplasty is used in conjunction with other therapies and less as a standalone treatment.¹⁸

2. **Atherectomy:** This procedure is also performed using a catheter inserted within the blood vessel to remove or debulk plaque and enlarge the internal opening of the artery (or lumen). It may be used alone, or in combination with balloon angioplasty, to facilitate the placement of stents or to improve patency without using a stent, or to improve drug absorption by removing plaque before the use of angioplasty and drug-coated balloons.^{8,19-21}

Atherectomy technologies debulk and remove plaque using different mechanisms, including cutting, shaving, drilling, sanding, or lasering.²² Many different atherectomy devices are commercially available.^{19,23,24} The type of blockage and location of the lesion can affect the choice of atherectomy device used.¹⁹ Some atherectomy devices are indicated for use only in the larger arteries above the knee, while other devices have smaller catheters that allow them to be used in the arteries below the knee.

Atherectomy devices are often categorized by the way in which they remove the plaque (Table 1).

Table 1: Types of Atherectomy Devices

Type	Description	Examples
Directional or excisional atherectomy	Plaque is removed by cutting in one direction and is captured in the nose cone or other part of the catheter and removed when the device is withdrawn. ²²⁻²⁴	TurboHawk [®] and SilverHawk [®] peripheral plaque excision systems (Medtronic). ^{23,25}
Orbital atherectomy	Plaque clears continuously as it is pulverized into tiny particles by the sanding action of the crown of the catheter as it spins in various elliptical orbits. ^{23,24}	Diamondback 360 Peripheral Orbital Atherectomy System (Cardiovascular Systems). ²⁶
Laser ablation (photoablative) atherectomy	Plaque is vaporized. ²³	Turbo-Elite [®] and Turbo-Tandem [®] excimer laser catheters, used with the CVX-300 excimer laser system* (Spectranetics). ^{23,25}
Rotational atherectomy	Plaque is cut using tiny blades on the tip, and in some systems, the neck or side, of the catheter, and aspirated into the catheter.	Jetstream Atherectomy System [®] (Boston Scientific). ^{19,22,23,25}

*Licenced in Canada.

The focus of this bulletin is on two of the many new endovascular devices:

- **Lithoplasty (Shockwave Medical)** – This is a technology that combines a balloon angioplasty catheter with the use of sound waves, similar to that used for kidney stones.²⁷ Calcified stenoses are more difficult to treat and the calcium deposits make the use of drug-coated balloons and stents less effective.^{27,28} Emitters on the Lithoplasty catheter deliver pulses of sound waves around the interior of the artery wall to break up superficial and deeper calcifications before angioplasty balloon inflation.^{15,29-32} The Lithoplasty system is intended to fracture calcifications and allow lower pressure balloon expansion, while minimizing damage to the artery wall.¹⁵ The system consists of a single-use balloon catheter with multiple lithotripsy emitters, and a reusable generator and connector cable.^{29,31}
- **Pantheris Lumivascular Atherectomy System** (Avinger, Inc.) – This is a directional atherectomy system that includes optical coherence tomography. Optical coherence tomography is an imaging technology (often used in eye exams) that uses light to provide three-dimensional visual guidance during the procedure (as opposed to two-dimensional X-ray images with fluoroscopy).^{21,33} The manufacturer suggests that this allows for better navigation to and removal of plaque, and reduces the risk of damage to the artery wall.^{21,34} Imaging guidance with optical coherence tomography may reduce the use of contrast agents, possibly allowing patients with kidney disease to receive treatment, and reduce exposure to radiation from fluoroscopic imaging guidance.^{21,34,35} The currently approved indication for the Pantheris system is as an adjunct to fluoroscopy.³⁶

The Pantheris system consists of the Pantheris catheter, occlusion sheath, Lightbox imaging sled, and Lightbox imaging console.²¹ The Pantheris catheter is 135 cm long with an optical fibre component for the optical coherence tomography.²¹ The nose cone of the catheter collects the excised plaque and tissue.²¹

Availability

Neither the Lithoplasty nor the Pantheris systems currently have Health Canada medical device licenses.²⁵

The Lithoplasty system received FDA 510(k) approval in 2016,^{31,37} and has been available in Europe since 2015.¹⁵ The approved US indication for the Lithoplasty system is for “... lithotripsy-enhanced balloon dilatation of lesions, including calcified lesions, in the peripheral vasculature, including the iliac, femoral, iliofemoral, popliteal, infra-popliteal, and renal arteries. Not for use in the coronary or cerebral vasculature.”^{31,37} The Lithoplasty system is not intended for the treatment of in-stent restenosis.²⁹ In Europe, the Shockwave Medical Coronary Rx Lithoplasty System is commercially available for the treatment of calcification in stenotic coronary arteries before the use of stents.^{38,39}

The Pantheris system received US FDA 510(k) approvals in 2015⁴⁰ and 510(k) approval of minor modifications in 2016.^{36,41,42} In the US, the approved indication for Pantheris is “to remove plaque (atherectomy) from partially occluded vessels in the peripheral vasculature with a reference diameter of 3.0 mm to 7.0 mm, using OCT-assisted orientation and imaging. The system is an adjunct to fluoroscopy by providing images of vessel lumen, wall structures and vessel morphologies. The Pantheris System is NOT intended for use in the iliac, coronary, cerebral, renal or carotid vasculature.”³⁶ The latest generation of the Pantheris system received the CE (Conformité Européenne) Mark, allowing it to be marketed in Europe, in December 2017, and the company now plans to file for US approval of the new system, which may also be used in below-the-knee procedures.^{34,43} According to the manufacturer, the new generation of the Pantheris system includes a simplified, single-balloon system, stiffer material to aid in insertion into the vessel, a sturdier nose cone with greater storage capacity, and an improved cutting tip.³⁴

Cost

The Canadian cost of these two devices is not yet known and no information on US costs was identified in the literature or provided by the manufacturers.

Who Might Benefit?

About 800,000 Canadians, or an estimated 4% of those over the age of 40, may have PAD.^{1,7} This is likely an underestimate as many people with PAD do not have documented symptoms and have not been diagnosed with the disease. PAD is more common in older people (affecting an estimated 20% of those over the age of 65).⁴⁴

Risk factors for PAD include diabetes, smoking, high cholesterol, and high blood pressure.¹⁰ Rates of diabetes and smoking are higher in low income communities.⁴⁵⁻⁴⁷

People with diabetes are at much higher risk for PAD.⁴⁸ Diabetic foot ulcers are mainly caused by chronic nerve damage (peripheral neuropathy) and ischemia resulting from peripheral vascular disease.^{49,50} About half of those with diabetic foot ulcers also have PAD — which both contributes to ulcer formation and further impedes wound healing, increasing the risk of amputation.^{10,51} Individuals with diabetes have a much greater risk of undergoing a lower limb amputation than those who do not have diabetes.⁵² Many amputations for PAD could be avoided through earlier diagnosis, preventive measures, and use of endovascular or surgical revascularization.^{5,53-55}

Current Practice

Diagnosis

A diagnosis of PAD usually requires the patient's clinical history, a physical examination, and a review of symptoms of claudication, along with an ankle-brachial index (ABI) test.^{10,56} The ABI, which generates a ratio blood pressure at the ankle versus arm, is usually the first diagnostic test used to detect PAD.^{10,57,58} Hand-held Doppler ultrasound may also be used to assess arterial blood flow.^{2,59} People with diabetes, kidney failure, or rheumatoid arthritis may have a falsely elevated ABI due to stiff arteries caused by calcification.³ For these individuals, a toe brachial index test or other diagnostic tests are needed.^{7,10,49,57,60} These measurements can indicate PAD, but not the precise location of a blockage, so further tests may be needed. This will likely require referral to a vascular laboratory for further testing, which may include: exercise testing (such as a treadmill or six-minute walking test), duplex ultrasound, segmental arterial limb pressures (blood pressure taken at various places on the leg), pulse volume recordings, and oxygen testing.^{2,8,12,53,57,61,62} Magnetic resonance angiography or computer tomography angiography, or more invasive angiography may also be needed to plan treatment.^{57,61}

The benefits of population-based screening for PAD is still an area of uncertainty, but screening is generally recommended for older adults with known cardiovascular risk factors, people with diabetes or symptoms of PAD, and all individuals over a certain age.^{12,56,58,63} The US Preventive Services Task Force is currently updating its 2013 recommendations on screening for PAD.⁶⁴

Leg ulcers may be caused by insufficient venous or arterial blood flow. Some patients will have both venous insufficiency and PAD, and determining the cause is necessary as treatments may differ.⁶⁵

Treatment

Initial therapy for PAD includes modification of cardiovascular risk factors — in particular, smoking cessation and dietary changes to reduce cholesterol and hypertension.^{7,61,66} Walking and supervised or home exercise programs are recommended to improve circulation, functioning, and quality of life.^{3,7,11,13,67} Drug therapies to control cardiovascular risk factors are also recommended, including drugs to control diabetes, hypertension, and cholesterol levels, as well as antiplatelet medications to prevent blood clots.^{7,56,59,61,68-70} For some patients with intermittent claudication, drugs such as pentoxifylline may be prescribed to improve blood flow in the legs.⁸ Many people with PAD do not receive appropriate risk factor modification therapies.^{3,70}

Early diagnosis and multidisciplinary care can reduce the progression of PAD, improve quality of life, and reduce the risk for amputation.^{71,72} Multidisciplinary care involves a formal care pathway that includes clinical experts in smoking cessation, hypertension, diabetes, podiatry, wound care, endovascular interventions, and vascular surgery.^{11,71,73}

Patients with severe PAD (disabling claudication or critical limb ischemia) may be treated with either endovascular therapy or vascular surgery. Which type of revascularization treatment is used, and the success of treatment, depends on the type of lesion (stenosis [narrowing] or total occlusion [blockage]), the location and length of the blockage, the amount of calcification, the amount of damage to the artery, and the patient's comorbidities and overall health.^{6,7,74,75} Not all patients have vascular access that can accommodate the use of endovascular techniques or lesions that can be treated with endovascular methods.^{7,23,56}

Endovascular Therapy

Endovascular, catheter-based therapies, including balloon angioplasty and atherectomy, are less invasive alternatives to vascular surgery that are usually performed as outpatient procedures by vascular interventional radiologists. Compared with vascular surgery, endovascular interventions avoid the need for general anaesthesia and have a shorter recovery

period.^{6,7} Although vessel patency may not last as long as that achieved with vascular surgery, endovascular procedures can be repeated if necessary.⁶ Both types of procedures carry risks, but endovascular options usually have fewer complications and also offer a treatment option for patients who are too frail to undergo general anaesthesia and surgery.^{6,16}

Endovascular therapies for PAD may also use drug-eluting stents and drug-coated balloons, or micro-infusion balloon devices to deliver drugs to prevent restenosis.³⁰ However, in-stent restenosis can result in renewed blockage.⁷⁶ In-stent restenosis may be treated with repeat balloon angioplasty, cutting balloon angioplasty, drug-coated balloon angioplasty, additional stents, or atherectomy.⁷⁶ All of these require crossing the blockage within the stent with a wire before the subsequent procedure can be performed.⁷⁶ Some atherectomy devices are approved for treating in-stent restenosis, but others are contraindicated for this indication.²³

Patients who undergo endovascular treatment for PAD may also receive anticoagulants and/or antiplatelet drugs to reduce the risk of thrombosis.^{23,77} Distal embolization (debris, such as a blood clot, tissue, plaque, or other material dislodged during the procedure that may obstruct blood flow) is a potential complication in endovascular interventions.⁷⁸ Embolization protection devices (filters) may be used to reduce this risk during the procedure.^{23,74} Use of these devices adds to the cost of the procedure and whether they are used appears to be at the discretion of the physician.⁷⁹ Antiplatelet drugs, such as clopidogrel, to prevent clotting may also be prescribed for one to six months after the treatment, followed by Aspirin monotherapy, but actual practice varies.^{11,78}

Vascular Surgery

Patients with severe PAD need an urgent referral to a vascular specialist, such as a vascular interventional radiologist or vascular surgeon.⁷ For some patients, vascular surgery may be needed to remove blockages or create a bypass around the blockage to improve blood circulation.^{7,59} As US clinicians noted in 2016: "... with few exceptions, all patients with CLI [critical limb ischemia] and salvageable limbs should receive an attempt at revascularization before amputation. If such expertise is not available, a referral to centres with such expertise should be considered."¹¹ The UK National Institute for Health and Care Excellence (NICE) guidance on PAD also recommends that, for patients with CLI, all revascularization treatment options for a patient should be assessed by a multidisciplinary team before considering amputation.⁵⁹

Methods

These bulletins are not systematic reviews and do not involve a detailed critical appraisal. They are not intended to provide recommendations for or against a particular technology.

Literature Search

A limited literature search was conducted on key resources including PubMed, The Cochrane Library and The University of York Centre for Reviews and Dissemination (CRD). Grey literature was identified by searching relevant sections of the Grey Matters checklist (<https://www.cadth.ca/grey-matters>). No methodological filters were applied. The search was limited to English-language documents published between January 1, 2012 and September 29, 2017. Regular alerts updated the search until project completion; only citations retrieved before February 28, 2018 were incorporated into the analysis. Conference abstracts were excluded from the search results.

Study Selection

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the intervention included treatments for PAD using the Pantheris or Lithoplasty systems.

Peer Review

A draft version of this bulletin was reviewed by three clinical experts. The manufacturers were also given the opportunity to comment on an earlier draft but neither provided comments or information.

The Evidence

In addition to the systems used for angioplasty and atherectomy, PAD procedures use various types of catheters, guidewires, stents (bare metal, drug-eluting, or covered), and angioplasty balloons (plain or drug-coated).^{8,16,76} Variations in the individual patient's vascular system, comorbidities, the experience and skills of the physician, and the many different auxiliary devices used, can also make it difficult to attribute outcomes to a particular technology. Several systematic

reviews have investigated the comparative effectiveness of different interventions (including endovascular therapies) for PAD, but the Lithoplasty and Pantheris devices were not included in these evaluations.^{16,80,81}

Lithoplasty Studies

For the Lithoplasty system we found one published report of the DISRUPT PAD I study,²⁷ a summary of the findings of the DISRUPT PAD trials to date (I and II) included in the US FDA 510k approval,³⁷ and a press release summary of the below-the-knee study,⁸² summarized in Table 2. Studies of Shockwave Medical's Lithoplasty balloon catheter for coronary artery disease (a case report³⁹ and a report on 31 patients in the DISRUPT CAD study²⁸) are not discussed here.

The DISRUPT PAD III study is ongoing.⁸³ DISRUPT PAD III is a randomized controlled trial which is currently recruiting patients (target sample size of 334) at 45 centres worldwide, with two-year follow-up of patients. It will compare Lithoplasty in combination with drug-coated balloon angioplasty to conventional balloon angioplasty with a drug-coated balloon.^{30,83} Up to 250 patients who do not meet the inclusion criteria for the PAD III trial will be enrolled in an observational study to obtain further "real-world" evidence.⁸³ Shockwave Medical is also investigating the use of Lithoplasty in the treatment of aortic valve stenosis (as an alternative to valve implantation), coronary artery stenosis, and PAD in below-the-knee arteries.^{15,38,39,84}

Table 2: Summary of the Evidence: Lithoplasty System

Study Name, Author, Publication Year, NCT #, Location	Patient Characteristics, Sample Size	Study Design and Funding	Intervention, Comparator	Outcomes	Key Findings
DISRUPT PAD I Brodmann M, et al. (2017) ²⁷ NCT02071108 Austria, New Zealand, Germany	n = 35 patients with moderate to severely calcified femoropopliteal lesions, average initial stenosis 76.3%, average lesion length 61.5 mm; severe calcification in 64.1% of patients; average calcified length of 80.3 mm	Single-arm, multi-centre, prospective study funded by Shockwave Medical	Lithoplasty with balloon angioplasty, with/without adjunctive angioplasty No comparator	Primary safety end point major adverse events to 6 months (see Safety section) Procedural success defined as < 50% residual stenosis with/without adjunctive angioplasty	< 50% residual stenosis achieved in all patients (residual stenosis averaged 23.4%) 100% vessel patency at 30 days, 82.1% patency at 6 months
DISRUPT PAD (I and II, 2 phase study) Summary of clinical data from US FDA 510(k) approval & company website (2016) ^{37,85} NCT02071108 NCT02369848 Austria, New Zealand, Germany	n = 95 patients with moderate to severe calcified femoropopliteal lesions (≤ 15 cm in length, Rutherford Category 2,3 & 4, severe calcification in about half of the patients)	Single-arm, multi-centre, prospective Funded by Shockwave Medical	Lithoplasty with balloon angioplasty, with/without adjunctive angioplasty No comparator	Primary safety end point major adverse events to 6 months (see Safety section) Procedural success defined as < 50% stenosis with/without balloon angioplasty	94 of 95 patients received Lithoplasty, target lesion patency achieved in 91.6% of patients, average patency at 6 months was 76.7%, average freedom from TLR at 6 months was 96.8% Functional outcomes, including walking, significantly improved at 6 months

Study Name, Author, Publication Year NCT # Location	Patient Characteristics Sample Size	Study Design and Funding	Intervention Comparator	Outcomes	Key Findings
DISRUPT BTK Summary from company press release Brodmann M, et al.(2017) ⁸² NCT02911623	n = 20 patients with moderate or severe calcification in arteries below the knee (80% had critical limb ischemia)	Prospective, single-arm, multi-centre Funded by Shockwave Medical	Lithoplasty with balloon angioplasty; No comparator	Primary safety end point major adverse events to 30-day follow-up (see Safety section) Procedural success defined as post Lithoplasty residual stenosis of $\leq 50\%$	Average residual stenosis post Lithoplasty was 27%

BTK = below the knee; ISR = in-stent restenosis; NCT = National Clinical Trial number; PAD = peripheral artery disease; TLR = target lesion revascularization.

Pantheris Studies

We found one published study of the Pantheris system (a final report of the VISION study),^{21,86} and a summary of case reports (Table 3).³⁵ Studies of Avinger's Ocelot optical coherence catheter for guidewire crossing of chronic total occlusions,^{87,88} and a report of one centre's experience with 11 patients from the VISION study⁸⁶ are not included here.

One ongoing, single-arm, multicentre trial was identified. The INSIGHT trial (Evaluation of the Pantheris Optical Coherence Tomography Imaging AtHemectomy System For Treatment of In-Stent Restenosis (ISR) Lesions In Lower Extremity Arteries) began in October 2017 and will be used to support a US FDA application for an expanded indication of treating in-stent restenosis in peripheral arteries.³⁴ The INSIGHT trial will enroll up to 140 patients at 20 centres in the US and internationally.^{34,89}

Table 3: Summary of Evidence for Pantheris

Study Name, Author, Publication Year NCT # Location	Patient Characteristics Sample Size	Study Design and Funding	Intervention Comparator	Outcomes	Study Author's Conclusions
VISION (Evaluation of the Pantheris Optical Coherence Tomography Imaging AtHemectomy System) Schwindt AG, et al. (2017) ²¹ NCT01937351 Germany and US	Patients with symptomatic, superficial femoropopliteal PAD 158 patients (87 men, average age 67; 133 were smokers, 69 had diabetes) 198 lesions, most (160) considered moderate & located in the SFA, average lesion length 53 mm, average stenosis 78.7%, 40 lesions (20.2%) were CTOs	Prospective, single-arm, multi-centre, investigational device exemption trial Funded by Avinger, Inc.	Pantheris catheter only, or Pantheris plus Adjunctive treatment ^a No comparator	Primary safety end point major adverse events to 6 months (see Safety section) Primary efficacy outcome (technical success) defined as % of target lesions with $\leq 50\%$ stenosis after Pantheris treatment only	$\leq 50\%$ residual stenosis in 192 of 198 target lesions treated with Pantheris (with or without adjunctive treatments) Average baseline stenosis 78.7% reduced to 30.3% with Pantheris only, and to 22.4% after Pantheris and adjunctive treatments

Study Name, Author, Publication Year NCT # Location	Patient Characteristics Sample Size	Study Design and Funding	Intervention Comparator	Outcomes	Study Author's Conclusions
	Exclusion criteria: moderate-severe calcifications, lesions within a graft or iliac artery, restenotic lesions, and acute ischemia or thrombosis			Procedural success defined as reduction in stenosis to $\leq 30\%$ after Pantheris plus adjunctive treatment	Fluoroscopy underestimated lesion length compared with measurement with Pantheris optical coherence tomography. Reliance on fluoroscopy only could result in under treatment of lesions
Lichtenberg MK, et al. (2017) ³⁵ Europe and US	<p>Patients with PAD and in-stent restenosis</p> <p>European patients: 21 patients at 6 centres; pre-procedural stenosis was 87%, average lesion length 172 mm, 67% of lesions had mild-to-moderate calcification, 67% of ISR lesions in the SFA, 14% in the popliteal, 14% in SFA and popliteal, and 5% in SFA and iliac arteries.</p> <p>US patients: 73 patients at 6 centres; average pre-procedural stenosis 84%, 47% of the lesions had mild-to-moderate calcification; 79% of ISR lesions in the SFA, 8% in SFA and popliteal, and remainder in tibial or popliteal and tibial arteries</p>	Summary of retrospective case series (presented within review article)	<p>European patients: Pantheris OCT-guided atherectomy^b</p> <p>US patients: Pantheris OCT-guided atherectomy^c</p> <p>No comparator</p>	<p>Adverse events (see Safety section)</p> <p>Procedural success defined as $< 30\%$ residual stenosis</p>	<p>European patients: procedural success achieved in all patients (average of 10% residual stenosis post Pantheris, and 5% final residual stenosis)</p> <p>US patients: treatment success achieved in 98.6% (72 of 73) patients, average of 20% residual stenosis post Pantheris</p>

CTO = chronic total occlusions; ISR = in-stent restenosis; NCT = National Clinical Trial number; OCT = optical coherence tomography; PAD = peripheral artery disease; SFA = superficial femoral artery.

^aadjunctive treatments: angioplasty with/without stenting at the discretion of the physician.

^b95% of patients also received adjunctive drug-coated balloon angioplasty; embolic protection devices were used in 76% of patients.

^cProcedure followed by percutaneous transluminal angioplasty in 25% of patients and drug-coated balloon angioplasty in 65% of patients; embolic protection devices were used in 72%.

Safety

Various complications may occur with endovascular procedures for PAD. These may be as a result of operator error or inexperience, device malfunction, or inappropriate (off-label) use of the device.²³

Common adverse events reported^{11,23} to be associated with endovascular procedures for PAD include:

- complications at the access site for the catheter, such as bleeding
- distal embolization (particularly with atherectomy)
- perforation
- dissection
- device entanglement (for catheters with rotating components), which can occur with existing stents, or in the fabric of stent grafts, or with the tissue lining the artery)
- injury caused by the guidewire
- infection.

Pantheris

In the VISION study, 25 of the 151 participants who completed the six-month follow-up experienced major adverse events.²¹ Six patients experienced seven device-related major adverse events: four clinically significant emboli, two dissections, and one pseudoaneurysm.²¹ Other adverse events were cardiovascular-related death (four patients), heart attack (three patients), and the need for target lesion revascularization (12 patients). The six-month target lesion revascularization rate was 7.9% in all participants, including those with chronic total occlusions.²¹ Less than 1% of lesion tissue (from 196 of the 198 lesions) analyzed post-procedure showed evidence of damage to the adventitia (the outer wall of the artery), which may confirm the value of optical coherence tomography in delineating plaque from the wall of the artery.²¹ Moreover, lesion length as determined with the Pantheris system was longer than that indicated by fluoroscopy, and treating the longer lengths may help to reduce the need for subsequent revascularizations.²¹

The summary of 94 German and US case reports on the use of Pantheris in patients with in-stent restenosis reported no serious adverse events, no embolisms that required further procedures, and no device-stent problems.³⁵

As of January 2018, the US FDA's MAUDE (Manufacturer

and User Facility Device Experience) database included 21 reports of problems that occurred when the Pantheris system was used.⁹⁰ Some problems were due to operator error or malfunctions of non-Pantheris devices used in the procedure (such as guidewires or embolic protection devices). Other reports included guidewires kinking or wrapping around and damaging the catheter or making it difficult to remove, catheter and embolic protection devices becoming stuck in the sheath, catheter entanglement in stents, and detachment of the nose cone of the catheter. Adverse events included several reports of dissection and embolization (when an embolic protection device had either not been used or had malfunctioned).

Lithoplasty

In the 35 patient DISRUPT PAD I study, assessed at 30 days and six months, there were no reports of major adverse events (defined as emergency surgical revascularizations, target limb amputation, thrombosis or embolization, or perforation or dissections requiring intervention).²⁷ No target lesion revascularizations were detected at six months.²⁷

In the DISRUPT PAD I and II studies, summary reports indicate that at 30 days follow-up, 97% of patients had not experienced a major adverse event (e.g., death due to cardiovascular causes, target limb amputations, or complications due to thrombus or distal embolization).³⁷ At six-month follow-up, 96.8% of participants were free from major adverse events (six-month follow-up included 93 of the 95 patients in the study).^{37,85} One perforation or dissection occurred using the Lithoplasty treatment (1.1%). Three target lesion revascularizations occurred within six months (3.2%).³⁷

A press release on the 20 patients in the below-the-knee PAD (DISRUPT BTK) study noted a low rate of vascular complications (one dissection), with no major adverse events (death, heart attack, target limb revascularization, or amputation) at 30 days follow-up.⁸²

The Lithoplasty system had a limited US commercial release in 2017.³² As of January 2018, there were no problem reports for the Lithoplasty system in the FDA's MAUDE database.⁹⁰

Cost Considerations

Atherectomy is typically used in addition to treatment with balloon angioplasty, so the Pantheris system would be an additional cost. The use of distal embolization filters is usually recommended with atherectomy procedures, and this would

be a further cost. There is limited evidence suggesting that the additional cost of atherectomy may be offset by reduced use of stents, however, the studies to date have not included the Pantheris system.⁹¹

Endovascular interventions for PAD are less expensive than bypass surgery, mainly because they reduce the need for operating room time, have fewer complications than surgical interventions, and may be performed as outpatient procedures (i.e., reduced hospital length of stay).^{51,54,92} However, the potential need for repeat procedures with endovascular procedures could reduce some of the cost difference.⁵¹

We did not find any cost studies of the Pantheris or Lithoplasty devices.

Concurrent Developments

Intermittent pneumatic compression is being used in some centres for people with CLI who cannot undergo revascularization procedures.⁹³ A recent meta-analysis concluded that this procedure may offer improved pain relief, wound healing, and limb salvage, but that, until better quality evidence is available, it should be considered “unproven.”⁹³

The SoundBite Crossing System (SoundBite Medical Solutions, Inc.), is another endovascular shockwave therapy system that is being investigated for chronic total occlusions in both coronary and peripheral arteries.^{94,95} Limited evidence also suggests that extracorporeal shockwave therapy (currently used for musculoskeletal pain, wound care, non-union fractures, and ischemic heart disease) may improve blood flow and reduce pain in individuals with intermittent claudication.^{44,96}

Many different catheter systems, drug-coated balloon angioplasty devices, and bioabsorbable (i.e., temporary) peripheral artery stents are also being assessed for their potential in preventing restenosis, reducing the risk of stent fractures and late thrombosis, and making future revascularization treatments possible.^{15,97-100}

An earlier Avinger device, the Ocelot, intended for crossing chronic total occlusions in peripheral arteries, also incorporates optical coherence tomography guidance.⁸⁷

Implementation Issues

Practitioner Learning Curve

The Pantheris VISION trial estimated that clinicians needed to perform five procedures before they were comfortable with using the technology.²¹ No information on the learning curve for the Lithoplasty system was found.

Barriers to Peripheral Artery Disease Care in Canada

We did not find any information on specific barriers to introducing the Lithoplasty or Pantheris systems into Canadian health care. However, in Canada, and elsewhere, PAD is often unrecognized, under-diagnosed, and under-treated.^{53,101} Barriers to detection of PAD include:

- lack of access to the equipment needed
- limited time for patient consults in general practice to allow for testing
- inadequate education and training of health care providers to test for the condition
- low level of public awareness to advocate for receiving testing.^{53,54,102}

A further barrier is limited funding for interventional radiology procedures, combined with increasing workload for interventional radiologists as more and more minimally invasive, endovascular treatments are used for a wide variety of conditions (Dr. Mark Baerlocher, Royal Victoria Hospital, Barrie, Ontario: personal communication, 30 Jan 2018).

Awareness and Prevention

A 2006 cross-sectional survey of 501 Canadian adults over age 50 found that one in three was aware of the condition.¹ More recently, a 2014 survey of 237 Toronto residents found almost 80% of those surveyed had never heard of PAD, and among those who had, there was little knowledge of disease symptoms, risk factors, and prevention.¹⁰³ Another Canadian study noted the need to increase education about PAD during medical training, including education on secondary prevention and rehabilitation.¹³ The authors also suggested that comprehensive prevention and treatment programs, similar to the Systematic Assessment of Vascular Risk (SAVR) program in Ontario,⁶⁸ should be available across Canada.¹³

The SAVR program successfully reduced the number of PAD-associated cardiovascular events (heart attack, stroke, and death) by 37%, and the number of limb amputations by 53% over a period of seven years.⁶⁸ The rate of angioplasties (with or without a stent) was three times higher in the SAVR intervention group — possibly because the participating physicians offered endovascular interventions sooner than at other centres, or because they were following their patients more closely, leading to earlier detection and treatment.⁶⁸

Peripheral Artery Disease and Diabetes

Early detection of PAD in individuals with diabetes is critical, but detection of PAD can be more difficult in those with diabetes, and screening tests may be less accurate.⁵¹ A recent Health Quality Ontario quality standard on venous leg ulcers highlighted several gaps in wound care management, including regular testing for individuals with PAD, or those who are at risk for developing venous leg ulcers.⁶⁵ Care for individuals with PAD is also linked to improving diabetic foot care.

Access to Multidisciplinary Care

Current guidelines stress the need for a multidisciplinary approach to treating PAD.^{56,75,101,104} However, many Canadians with PAD, particularly those outside of urban centres, lack timely access to integrated care teams that include expertise in diabetes, wound care, podiatry, nutrition, physiotherapy, vascular interventional radiology and vascular surgery.⁵⁴ Lack of multidisciplinary care can contribute to reduced patient quality of life, higher rates of potentially preventable amputations, and increased health care costs.⁵⁴

Access to Interventional Radiology Technologies and Catheterization Laboratories

In Canada, vascular and interventional radiologists typically perform endovascular procedures for PAD. Increasingly, vascular surgeons are also performing these endovascular procedures.⁹² A recent report on interventional radiology in Canada noted that interventional radiology procedures, performed in a catheterization laboratory, offer cost savings through reduced use of hospital operating rooms, and either a shorter length of stay or through performing the procedure as an outpatient procedure.⁹² But, relative to other developed countries, Canada has lagged behind in adopting interventional radiology procedures, including those for the treatment of PAD.⁹² In 2013, only an estimated 2% of patients diagnosed and treated for PAD

in Canada received endovascular treatments, compared with 12% in the US, and 6% in Europe.⁹²

Reduced Exposure to Radiation

The Society of Interventional Radiology and the Society for Vascular Surgery guidelines note increasing levels of ionizing radiation exposure for both patients and health care providers — due to the increasing numbers, complexity, and duration of interventional procedures that require fluoroscopic guidance.^{8,105-107} As a safety issue, radiation exposure should be recorded in each patient's medical record and reported by studies of these interventions.^{8,105} Shorter fluoroscopy times were noted in the Pantheris VISION study (on average a reduction of five minutes between new users and experienced users of the technology), which suggests it may be possible to reduce radiation exposure after the initial learning curve, but comparisons of exposure times with different endovascular technologies are needed.²¹

Final Remarks

Currently, there is limited evidence on both the Pantheris and the Lithoplasty systems. This is not unique to these two technologies — recent guidelines and systematic reviews have noted the poor quality of evidence on atherectomy and many of the newer endovascular treatments for PAD.^{16,80,81,108} Some of the shortcomings in evidence may be addressed by the ongoing trials of Pantheris (INSIGHT) and Lithoplasty (DISRUPT PAD III). Further evidence gaps may be filled by the Best Endovascular versus Best Surgical Therapy for Patients with Critical Limb Ischemia (BEST-CLI) trial, which includes centres across Canada and the US and is expected to end in December 2019.^{109,110} The trial includes various endovascular technologies and will follow patients for at least two years to assess survival, amputation rates, quality of life, and the cost-effectiveness of the different treatments.¹⁰⁹

The Peripheral Academic Research Consortium explained that comparisons between treatments for lower extremity PAD are difficult for various reasons, including:⁹

- the lack of standardized terminology and different classification systems used to describe the patient's condition and type of lesion
- the multiple interventions and imaging methods used
- inadequate reporting of outcomes, and different methods of measuring procedural success in the clinical trials.⁹

Further complicating assessments of the evidence are the differing combinations of devices and interventions used in endovascular PAD interventions, and limited comparative evidence available.³⁰

During an interview, the 2016 American Heart Association (AHA)/ American College of Cardiology (ACC) Task Force Guideline Writing Committee on Management of Patients with Lower Extremity Peripheral Artery Disease concluded that PAD: "... remains understudied relative to other cardiovascular diseases, and many evidence gaps remain."¹¹ Similarly, the 2015 Society for Vascular Surgery Practice Guidelines for Atherosclerotic Occlusive Disease of the Lower Extremities Guidelines on the Management of Asymptomatic Disease and Claudication notes that evidence from good quality studies that include outcomes important to patients is needed to guide decision-making in PAD.¹²

In Canada, there is interest in improving awareness of screening, preventive interventions, access to treatments, and rehabilitation strategies for people with PAD. A recent Canadian commentary noted that, in addition to educating clinicians to screen their patients for PAD and providing support to high-risk individuals, "a directory of resources available to help treat patients" would be useful.⁵³ Similarly, Alberta researchers who conducted a 2016 review of rehabilitation therapy for PAD noted the need for a survey of PAD rehabilitation programs across Canada to identify service gaps.¹³

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